Remarks

I. Examiner's Grounds for Rejection

In the Office Action, the examiner variously rejected pending claims 1-79 and 81-109 under 35 USC §112, second paragraph, for asserted indefiniteness, and under 35 USC §112, first paragraph, for assertedly lacking enablement and written description in the specification. The claims were also variously rejected under 35 U.S.C. §103(a) as follows: claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79, and 109 as obvious over Shan et al., *J Immunol* 162:6589-95, 1999 (hereinafter "Shan") in view of Pluckthun, US Patent 6,815,540 (herinafter "Pluckthun"); claims 1, 56, 65, 70-72 under 103(a) as obvious over Shan and Pluckthun in view of Bodmer, US Patent 5,677,425 (hereinafter "Bodmer"); claims 1, 63, 66, and 82 as obvious over of Shan and Pluckthun further in view of Bodmer and Morrison, US Patent 6,284,536 (hereinafter "Morrison"); and claims 1, 64, 67, 73-75, 77 and 81 as obvious over Shan and Pluckthun further in view of Roux et al., *J Immunol* 161:4083-90, 1998 (hereinafter "Roux").

Applicants respectfully request reconsideration in light of the amendments and response filed herein.

II. Support For Amendment to the Claims

Support for new claim 110 can be found, for example, at page 224, lines 3-12, of the substitute specification filed June 8, 2007, which describes the construct G28-2V_HL11S (SSC-P) H WCH2WCH3 as set out in SEQ ID NO: 329. The amendment includes no new matter.

III. The Rejection of Claim 13 under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

The examiner maintained the rejection of claim 13 for the recitation of the term "des-leucine." As stated previously, the designation "des" preceding the name of the amino acid indicates that that particular amino acid has been deleted and no amino acid has been substituted in its place This designation is used frequently in the art. See, for example, p 555, col. 1, of *J Biol Chem* 242:555-557, 1967, submitted herewith as Exhibit A, which was inadvertently omitted from Applicants previous response.

IV. The Rejection of Claims 29, 30 and 83-108 under 35 U.S.C. §112, First Paragraph-Enablement, Should Be Withdrawn

The examiner maintained the rejection of claims 29-30 and 83-108 under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The examiner asserts that the specification does not teach that the hybridomas set out in the claims are readily available to the public and reiterated the suggestions for biological deposit of hybridomas.

The claims are directed to a binding domain fusion protein which comprises a variable region binding domain of particular named hybridomas. The claims do not require the sequence of the entire hybridoma genome, but rely only on the sequence of the variable region binding domains, for which the sequences are specifically set out in the application. The remainder of the binding domain fusion protein comprises an immunoglobulin connecting region and immunobglobulin constant regions, for which sequences are also provided in the application. The specification has described the sequences of the variable regions of the hybridomas sufficiently such that they are readily reproducible by those of ordinary skill and can be combined with the Ig sequences disclosed herein to arrive at the present invention. Therefore, the specification allows one of ordinary skill to make and use the invention by providing the sequence of the fusion protein having the sequence of the

variable regions of the antibodies produced by the hybridomas set forth in the claims, the sequence of the connecting region, and the sequence of the Ig constant regions. Additionally, given the availability of the variable region sequences in the application and techniques for recombinant protein production known in the art and taught in the specification, a person of ordinary skill has the necessary tools to make modifications, such as amino acid substitutions, deletions, etc., to the variable region sequences of the hybridomas recited in the claims.

Because the sequences needed to make and use the binding domain fusion proteins of claims 29, 30 and 83-108 are disclosed in the application and publicly available, and one of ordinary skill could readily make and use a fusion protein as claimed based on the disclosed sequences, the deposit of the hybridomas set out in the claims is not necessary. As such, the rejection under 35 U.S.C. §112, first paragraph, enablement, should be withdrawn.

V. The Rejection of Claims 1-28, 31-58, 61-79 and 81, 82 and 109 under 35 U.S.C. §112, First Paragraph-Enablement, Should Be Withdrawn

The examiner maintains the rejection of claims 1-28, 31-58, 61-79 and 81, 82 and 109 under 35 U.S.C. §112, first paragraph, as assertedly lacking enablement for a binding-domain Ig fusion protein having specificity for any antigen or which comprises any amino acid substitution or deletion in position 9, 10, 11, 12, 108, 110, 112 in the VH region or amino acids 12, 80, 81, 83, 105, 106, and 107 in the VL region.

The examiner acknowledges that the application does enable substitutions at VH amino acids 9, 10, 11, 123, 108, 110 and 112 or amino acids 12, 80, 81, 83, 105, 106, and 107 in the VL region for the amino acids listed in the specification. However, the examiner contends that Applicants have not taught which modifications could be predictably made and which choice is likely to be successful.

The Examiner cites the Federal Circuit's *Wands* decision and cites the "*Wands* factors," as the guideline for determining enablement. *Wands* involved an invention that required screening of large numbers of hybridomas to identify specific hybridomas that fell within the claim limitations. Because the patentee in *Wands* provided sufficient guidance to make and screen the hybridomas and presented working examples, the Court found that the enablement requirement was fulfilled. *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). In reaching a decision, the Court in *Wands* considered that the inventor's disclosure provides considerable direction and guidance on how to practice the invention and presents working examples, and does not hold that a specific number of working examples is required. *Id* at 740. This fact, coupled with the high level of skill in the art, renders the invention enabled in the courts' opinion. *Id.* Although a considerable amount of work may have been required to do the making and screening, such experimentation is routine, not "undue," according to *Wands*. The *Wands* decision (a finding of successful enablement) was not based on a consideration of whether the inventors had identified which amino acids were critical to their invention and which could be changed, but rather, was based on the fact that the inventors had enabled a person of ordinary skill to make candidates and identify satisfactory molecules using routine screening. The court held that the need for routine screening to practice variations of the invention does not negate enablement.

With respect to the guidance in the present specification relating to substitutions in the variable region, paragraph 346 describes several publications which describe methods of engineering framework regions and CDR in the antibody variable region, and methods to achieve functional antibodies after modification of these regions, teaching that areas that are in contact with other domains of the antibody (e.g. CH1 or VL if a heavy chain variable region) may be altered in single chain proteins of the present invention

not having these binding needs. Additionally, WO92/01787 and WO98/02462 describe residues of the variable regions in which amino acid substitutions may be made. Further, the specification teaches methods for determining whether the constructs having mutations in any one of these amino acid residues are functional, such as assessing binding to cells expressing the antigen of interest (see Example 2), and Examples 20, 34, 35, 38, 41 and 42 demonstrate that constructs of the invention, which are specific to various target molecules such as CD20 and CD37, bind their respective target antigen and exhibit effector function. The methods disclosed may be used to assess binding and effector function of any molecule of interest. As such, the current disclosure teaches methods for making the sequence alterations, methods for screening the effector function of the molecules which are routine in the art, and provides working examples of constructs of the invention. One of ordinary skill can readily make and use the invention with some experimentation but without undue burden using routine techniques, similar to the facts of the case in *Wands*.

The examiner asserts that Applicants did not address the art cited that relates to predictability in the art with respect to amino acid substitutions. Applicants acknowledge the art and assert that the claims are directed to changes in specific amino acid residues in the VH or VL region and not to <u>any</u> amino acid change at <u>any</u> position in the variable region as the examiner appears to suggest. A worker of ordinary skill does not need to try to imagine which amino acid residues to change, since the claims specify which amino acid(s) is to be changed. As such, the change in the amino acid is predictable as there are a limited number of choices to which a single amino acid can be altered. Moreover, the residues in an immunoglobulin variable region are highly conserved such that the worker of ordinary skill can readily determine which residues in a variable region are within domains that may be altered. See e.g., Kabat et al. ((1991) Sequences of Proteins of Immunological Interest , 5th

Ed. , Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD) which describes the conserved residues in the framework and CDR regions. As such, variations at the amino acid residues recited in the claims may be made in antibody variable regions without undue experimentation.

Given the high level of skill in the art of recombinant protein engineering, coupled with the teaching in the specification of methods to modify antibody variable regions, methods of screening for binding affinity, and working examples of the constructs of interest having a variable region with at least one amino acid change, one of ordinary skill would be able to make and use a construct of the invention comprising a mutation in either a heavy chain or a light chain variable region in an claimed fusion protein without undue experimentation. Therefore, the rejection of claims 1-28, 31-58, 61-79 and 81, 82 and 109 as lacking enablement under 235 USC 112, first paragraph, should be withdrawn.

The examiner further asserts that claims 29, 30 and 83-108 can be interpreted to read on scFvs having modifications in the variable region which are produced by hybridomas recited in the claims and in the specification, and suggests biological deposit of the hybridomas. This rejection has been addressed in Section IV above.

For the reasons stated above, the rejection of claims 1-28, 29, 30, 31-58, 61-79 and 81, 82 and 83-109 under 35 U.S.C. §112, first paragraph, as assertedly lacking enablement, should be withdrawn.

VI. The Rejection of Claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79 and 109 under 35 U.S.C. §103(a) Should Be Withdrawn

The examiner rejects claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79 and 109 under 35 U.S.C. §103(a) as allegedly obvious over Shan

and Pluckthun. The examiner contends that Shan teaches that the constructs it discloses "are amenable to further structural modification" (see page 13 of the Action) and asserts that it would be obvious for one of ordinary skill in the art to take a protein construct of Shan and modify the protein according to the teachings of Pluckthun.

The rejected claims are dependent from either claims 1 or 77 which are directed to a single chain protein having a binding domain comprising a heavy chain variable region with a modification at position 11 in the heavy chain variable region.

Shan discloses an scFv specific for the CD20 molecule further comprising an hinge, CH2 and CH3 region of the IgG1 antibody. Shan teaches that the length of the linker region in the scFv construct plays a role in the affinity and aggregation of the protein. Shan teaches that additional "structural modifications are underway to generate dimeric scFv which may prove superior to the present constructs" (Page 6594, col. 2). Shan communicates in the "Discussion" section (pp 6593-94) that the monovalent antibody tested is not as efficient as the bivalent antibody, describes failed attempts at making bivalent Fab constructs, and suggests the use of recombinant methods to make smaller antibodies with intact bivalent binding properties (col. 1 p 6594). Shan does not disclose or suggest a construct having a change in the heavy chain variable region, and especially not a change at position 11.

The examiner asserts that Shan is neither limited to the kind or extent of the modification. Shan, however, states that the structural modification would be to construct a dimeric molecule, and neither discloses nor suggests structural modifications in terms of modification of the variable region to obtain increased expression. Pluckthun does not provide motivation in view of Shan to modify the variable regions since Shan discusses

modification of regions useful to make dimeric molecules and would not be looking to the disclosure of Pluckthun relating to increased protein solubility.

Pluckthun teaches that residues in the variable region of an antibody may be altered to potentially provide stability and increased recombinant expression of the engineered antibody. Pluckthun describes 16 possible residues in each of the heavy chain and light chain variable region that may be mutated (col. 5, line 66, to col. 6. line 4) and describes the generation of several scFv having one or more mutations in the residues set out in the description. Pluckthun teaches that changes in position 11 to asparagine show nearly no effect on increased solubility while substitution with aspartic acid has some effect, but not a very dramatic effect. Pluckthun then teaches that alteration of residues 84, 87 and/or 89 imparts dramatically improved solubility properties (col. 11, lines 20-59).

A worker of ordinary skill in the art reading Shan in view of Pluckthun would not be motivated to generate a construct having a mutation at position 11 in the heavy chain variable region to improve protein expression. Of the sixteen possible residues that could be changed in Pluckthun, changing amino acid residues other than position 11 are the optimal changes to achieve the desired goal (e.g., change at position 84 is the best). One of ordinary skill reading Shan would not be motivated to generate a modified construct having a VH modification at position 11 when Pluckthun teaches toward other modifications.

Additionally, the present specification demonstrates that changing the leucine at position 11 in a single chain protein of the invention improves the expression levels of the modified protein (paragraph 632, Example 34), which is unexpected given the results taught in Pluckthun. One of ordinary skill reading Shan in view of Pluckthun would not reasonably expect that a change at position 11 would improve solubility.

For the reasons set out above, a person of ordinary skill in the art would not be motivated by Pluckthun to modify residue 11 in the VH region in a construct set out in Shan to arrive at a single chain protein with improved production, and the rejection of claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 66, 65, 68, 69, 71, 72, 76-79 and 109 under §103(a) as obvious over Shan in view of Pluckthun should be withdrawn.

VII. The Rejection of Claims 1, 56, 65 and 70-72 under 35 U.S.C. §103(a) Should Be Withdrawn

The examiner maintained the rejection of claims 1, 56, 65, and 70-72 under 35 U.S.C. §103(a) as allegedly obvious over Shan and Pluckthun further in view of Bodmer.

The claims are directed to a single chain protein having a binding domain comprising a variable region with a modification at residue 11, further wherein the Ig region is humanized (claim 56), wherein the connecting region comprises a human IgG1, IgG2, IgG3 or IgG4 hinge region having either zero or one cysteine residue (claim 65) or wherein the connecting region has one cysteine residue, comprises no more than one cysteine residue or wherein the connecting region is altered so that said protein has a reduced ability to dimerize (claims 70-72).

Shan and Pluckthun have been described above. Bodmer describes a tetrameric antibody construct comprising variable regions, a hinge, CH1, CH2 and CH3 regions, wherein the altered antibodies have a reduced number of cysteine residues in the hinge region. Bodmer further discloses that the variable regions of the antibody may be humanized. Bodmer neither discloses nor suggests a construct having the structure of the claimed constructs, nor modification of position 11 of the heavy chain variable region.

As stated above, a worker of ordinary skill in the art reading Shan in view of Pluckthun would not be motivated to generate a construct of the invention having a modification at residue 11 in the VH region. Further, a person of ordinary skill in the art reading Bodmer in view of Shan and Pluckthun would not have been led to the single chain proteins recited in claim 1 because none of the three references provide motivation to produce a single chain protein having the structure of the claimed proteins possessing a modification at position 11 of the VH as claimed.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness for any of the rejected claims and the rejection of claims 1, 56, 65 and 70-72 under 35 U.S.C. §103(a) as obvious over Shan and Pluckthun in view of Bodmer should be withdrawn.

VIII. The Rejection of Claims 1, 63, 66 and 82 under 35 U.S.C. §103(a) Should Be Withdrawn

The examiner maintained the rejection of claims 1, 63, 66, and 82 under 35 U.S.C. §103(a) as allegedly obvious over Shan and Pluckthun further in view of Bodmer and Morrison.

The claims are directed to single chain proteins of the invention comprising a VH domain having a modification at position 11, further comprising an IgA hinge region, which may modified to contain a particular number of cysteine residues.

Shan, Pluckthun and Bodmer have been described above. Morrison describes modified antibodies having various domains of an IgA antibody, including the hinge, CH1, CH2 or CH3 region of IgA. Morrison neither discloses nor suggests modification of the variable regions to improve protein production or yield or for any other reason.

As stated above, a worker of skill in the art reading Shan in view of Pluckthun would not be motivated to generate a construct of the invention having a modification at residue 11 in the VH region. A person of ordinary skill in the art reading Morrison in view of Shan, Pluckthun and Bodmer would not have been led to the single chain proteins recited in claim 1 because none of the references provide motivation to produce a single chain protein having the structure of the claimed proteins possessing a modification at position 11 of the VH as claimed.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness for any of the rejected claims and the rejection of claims 1, 56, 65 and 70-72 under 35 U.S.C. §103(a) as obvious over Shan and Pluckthun in view of Bodmer further in view of Morrison should be withdrawn.

IX. The Rejection of Claims 1, 64, 67, 73-75, 77 and 81 under 35 U.S.C. §103(a) Should Be Withdrawn

The examiner maintained the rejection of claims 1, 63, 66, and 82 under 35 U.S.C. §103(a) as allegedly obvious over Shan and Pluckthun further in view of Roux.

The claims are directed to single chain proteins having a binding domain comprising a heavy chain variable region with a modification at residue 11, further comprising a hinge region derived from either IgE or IgG1, and wherein the connecting region comprises three cysteine residues and one proline residue.

Shan and Pluckthun have been described above. Roux describes antibodies having IgE and IgG1 hinge regions and describes generating hinge regions having proline substitutions at the cysteine residues. Roux neither discloses nor suggests modification of the

variable regions nor discloses a single chain protein having the structure of the claimed proteins.

As stated above, a worker of skill in the art reading Shan in view of Pluckthun would not be motivated to generate a construct of the invention having a modification at residue 11 in the VH region. A person of ordinary skill in the art reading Roux in view of Shan and Pluckthun would not have been led to the single chain proteins recited in claim 1 because none of the three references provide motivation to produce a single chain protein having the structure of the claimed proteins possessing a modification at position 11 of the VH as claimed.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness for any of the rejected claims and the rejection of claims 1, 56, 65 and 70-72 under 35 U.S.C. §103(a) as obvious over Shan and Pluckthun further in view of Roux should be withdrawn.

X. .Conclusion

Applicants submit that the application is in condition for allowance and request notification of the same.

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Respectfully submitted,

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